National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Radiation Workers

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Radiation Epidemiology Course
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Radiation Worker Studies

- **Nuclear workers exposed to low doses of external radiation**

- **Mayak nuclear workers**
  - **Exposed to high protracted external doses**
  - **Plutonium**

- **Medical and dental workers**

What is a Nuclear Worker?

What is a Nuclear Worker?

Involved in the

- **production of nuclear power**
- **manufacture of nuclear weapons**
- **enrichment and processing of nuclear fuel**
- **reactor or weapons research**

Does not include medical and dental workers or underground miners

Why study nuclear workers exposed to low doses of external radiation?

- Current risk estimates based on A-bomb survivors and others exposed at high dose rates
- For risk assessment, interest is primarily in low doses and dose rates
- Uncertainty in the extrapolation process

Why study workers?

- Dose estimates obtained from personal dosimeters worn by workers
- Exposures deliberately limited as a protection to the worker
- Provide a direct assessment of risks at low doses and dose rates
- Limitations, but worker studies can detect serious underestimation of risk

Magnitude of Doses

Current risk estimates:

Driven by doses of 0.5+ Gy

Worker-based estimates:

Driven by doses 0.1-0.5 Gy

Of interest for risk assessment:

0 - 0.1 Gy

Predicted relative risks* for adult male exposed at low dose rate

Dose	Solid cancers	Leukemia
1 Sv	1.2	2.4
0.5 Sv	1.1	1.7
0.2 Sv	1.03	1.3
0.1 Sv	1.02	1.1
0.01 Sv	1.002	1.01

*Based on BEIR VII models developed from A-bomb survivor data

History of Studies of Workers at Individual Facilities

Population	Country	Publication Date(s)
Hanford Site	US	1978, …, 1993
Oak Ridge Nat'l Lab.	US	1985, 1991
Atomic Energy Authority	UK	1985, 1993
Sellafield Plant	UK	1986, 1994, 1999
Rocky Flats Weapons Plant	US	1987
Atomic Energy of Canada	Canada	1987
Atomic Weapons Establish.	UK	1988
Savannah River Plant	US	1988, 1999
Mound Laboratory	US	1991
Los Alamos Nat'l Lab.	US	1994
Rocketdyne	US	1999, 2006
Mallinckrodt Chemical	US	2000

History of Studies of Workers

Population	Country	Publication Date
National Registry of Radiation Workers	UK	1992, 1999
National Dose Registry	Canada	1998, 2001
Nuclear reactor workers	Finland	2002
Nuclear industry workers	Japan	1997, 2003
Nuclear power workers	US	2004
Nuclear power workers	Canada	2004
Atomic Energy Commission	France	2004
National Electricity Co.	France	2005
Nuclear workers	Belgium	2005
Idaho National Engineering and Environmental Lab.	US	2005
Nuclear industry workers	Australia	2005

Approaches to Analyses

External Comparisons:

- **Compare cause-specific death rates with national rates (SMRs)**

Internal comparisons:

- **Compare cause specific death rates by level of cumulative radiation dose**

Standardized Mortality Ratios (Numbers of Deaths)

Population	All Causes	All Cancers
United States:		
Hanford Site	0.82 (9,452)	0.86 (2,195)
Oak Ridge	0.74 (1,524)	0.79 (346)
Rocky Flats	0.62 (409)	0.71 (95)
Mound	0.79 (309)	0.88 (66)
Los Alamos	0.63 (3,196)	0.64 (732)
Savannah River	0.78 (1,722)	0.82 (413)
Rocketdyne	0.68 (844)	0.79 (248)
Mallinckrodt	0.90 (1,013)	1.05 (283)

Approaches to Analyses

External Comparisons:

Compare cause-specific death rates with national rates (SMRs)

Internal comparisons:

Compare cause-specific death rates by level of cumulative radiation dose

Internal comparisons

- **Linear relative risk model:**

  RR = 1 + B dose, where B = ERR/Sv

- **Choice of models driven by findings from A-bomb and other high dose studies**

Results of Dose-Response Analyses for Studies of Individual Facilities

- **All cancers:** Most studies consistent both with no risk and risks several times those predicted from high dose studies
- **Leukemia:** Significant dose-response in some but not all studies.
- **Site-specific cancers:** No consistent pattern across studies

Combined Analyses

- Obtain more precise estimates of risk
- Opportunity for understanding differences and similarities in studies
  - Comparable statistical methods
  - Results in comparable format
- Best overview or summary of studies

Combined Studies of Workers

Population	Country	Publications
Hanford/Oak Ridge/Rocky Flats	US	1989, 1993
AEA/AWE/Sellafield	UK	1994
IARC* 3-country	US/UK/Canada	1994, 1995
IARC* 15-country		2005, 2007

- 96,000 workers in the US, UK, and Canada

*International Agency for Research on Cancer

Two Large Worker Studies

- **15-country study**
  - **Coordinated by the International Agency for Research on Cancer (IARC)**

    Cardis et al. 2005; 2007

- **National Registry of Radiation Workers (NRRW) in the UK**

  Muirhead et al. 2009

- **Most exposure received by males**

IARC* 15-Country Nuclear Worker Study

- 407,391 workers (after exclusions)
  - 90% male
  - Includes most workers in previous studies in US, UK, and Canada
  - Several new studies in US and other countries
- Mean cumulative dose of 19.4 mSv
- Collective dose of 7892 person-Sv

*International Agency for Research on Cancer

Cardis et al. 2005

IARC 15-Country Study

- **Main findings published in British Medical Journal (Cardis et al. 2005)**

- **3 papers published in Radiation Research**
  - **Cancer risks (Cardis et al. 2007)**
  - **Methods (Vrijheid et al. 2007)**
  - **Dosimetry (Thierry-Chef et al. 2007)**

15-Country Study (Cancer deaths)

United States (2,841)
United Kingdom (2,273)
Japan* (432)
Canada (417)
France (348)
Sweden (194)
Belgium (90)
Hungary (40)
Finland (34)
Lithuania (25)
Spain (25)
Korea (21)
Switzerland (24)
Australia (20)
Slovakia (10)

*Included only in leukemia analyses

Cardis et al. 2005

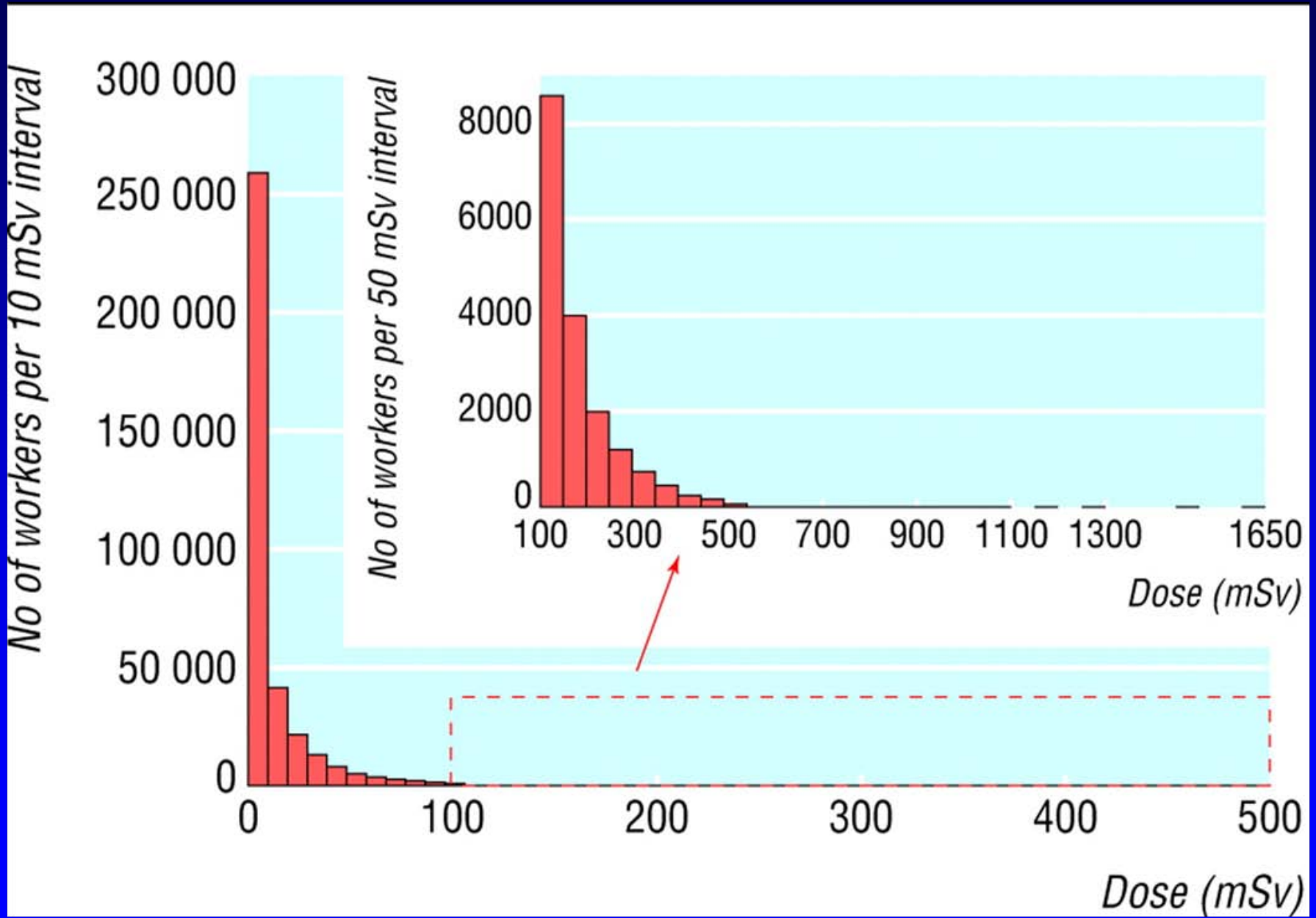
Dosimetry for 15-Country Study

- **Extensive attention given to dosimetry**
  - **Dosimetry subcommittee**
  - **Questionnaires on dosimetry practices and radiation environments**
  - **Special studies of representative facilities**
  - **Testing of several representative dosimeters**

- **Objective: Develop factors for converting recorded doses to organ doses and evaluate uncertainties in these factors**

Thierry-Chef et al. 2007

Cumulative Dose Distribution



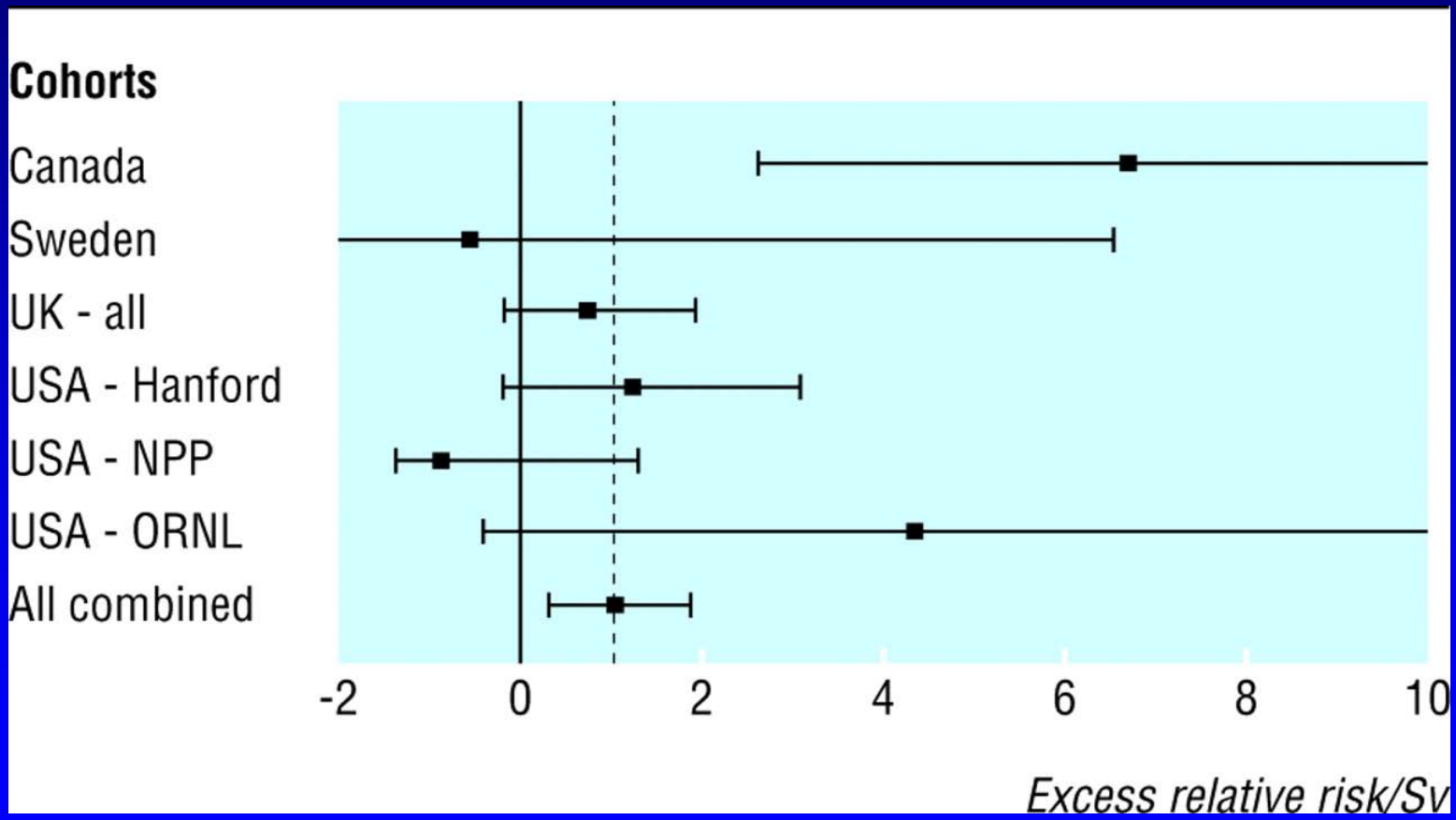
15-country Study: ERR/Gy (90% CI)

	All cancer excluding leukemia	Non-CLL Leukemia
15-country	0.97 (.27, 1.8)	1.9 (<0, 7.1)
A-bomb survivors*	0.26 (0.14, 0.41) (linear)	1.4 (0.1, 3.4) (linear-quadratic)

*BEIR VII for adult males

Cardis et al. 2007

15-Country Study: ERR/Gy



Cardis et al. 2005

Heterogeneity Among Countries All Cancer Excluding Leukemia

- p-value for heterogeneity = 0.18
- Estimate with all countries: 0.97 (0.14, 2.0)
  Estimate with Canada excluded: 0.58 (–0.2, 1.6)
- Estimate remained statistically significant when other studies were excluded individually

Cardis et al. 2005

Excess Relative Risk (ERR) per Gy for 15-Country Study

All solid cancers (4770)	0.87 (0.02, 1.9)
Solid cancers unrelated to smoking (2033)	0.62 (–0.5, 2.2)
Smoking related cancers (2737)	0.91 (–0.1, 2.2)
Lung cancer	1.85 (0.26, 4.0)
Other smoking-related cancers	0.21 (< 0, 2.0)

Cardis et al. 2005

Comments on 15-Country Nuclear Worker Study

- Generally well-conducted study
  - Strong dosimetry
- Common core protocol set out details of study including
  - Which workers to be included
  - How analyses to be conducted
- Subject to limitations of low dose epidemiologic studies
  - Likely bias due to confounding by smoking
  - Possible problems with Canadian data

National Registry of Radiation Workers (NRRW)

- 175,000 workers at several selected facilities in United Kingdom
- 87,300 of these workers also in IARC 15-country study
- Both mortality and cancer incidence data

Muirhead et al. 2009

Characteristics of Two Large Worker Studies

	Number of workers	Total person-Sv	Av. Dose (Sv)	Number of cancers
15-country	407,391	7,892	0.019	5,024
NRRW	174,541	4,348	0.025	8,107

Large Worker Studies: ERR/Gy (90% CI)

	All cancer excluding leukemia	Leukemia excluding CLL
15-country	0.97 (0.27, 1.8)	1.9 (<0, 7.1)
NRRW	0.28 (0.02, 0.6)	1.7 (0.1, 4.3)
A-bomb survivors*	0.26 (0.14, 0.41) (linear)	1.4 (0.1, 3.4) (linear-quadratic)

*BEIR VII for adult males

Large Worker Studies: Non-cancer Mortality

- **15-country study**
  - **Little evidence of dose-response relationship**
  - **Suggested dose-response for attained ages under 50**

Vrijheid et al. 2007

- **NRRW**
  - **Dose-response relationship for circulatory disease mortality**
  - **Possible confounding by smoking**

Muirhead et al. 2009

Limitations of Low Dose Worker Studies

- Increase in risk likely to be at most a few percent
- Low statistical power and imprecisely estimated risks
- Strong potential for confounding

What is the Role of Low-Dose Nuclear Worker Studies?

- Most informative of studies of persons exposed at low doses and dose rates
- Statistical uncertainties and high potential confounding impose important limitations

Radiation Worker Studies

- Nuclear workers exposed to low doses of external radiation

- Mayak nuclear workers
  - Exposed to high protracted external doses
  - Plutonium

- Medical and dental workers

Mayak Nuclear Facility

- Located in the town of Ozyorsk (formerly Chelyabinsk-65) in the Chelyabinsk region of the Russian Federation
- Began operations in 1948
- Mission was to produce plutonium for USSR nuclear weapons program
- Large exposures to both workers and general public, mostly in the 1940’s and 1950’s

Mayak nuclear facility

Mayak Worker Cohort

- 26, 000 workers hired 1948-82
- 25% female
- 13,000 deaths
- 3,000 deaths from cancer

- Exposed to both external radiation and to plutonium

- Protracted low dose rate exposure similar to that of interest for radiation protection

Gaps Filled by Mayak Worker Cohort

- **Large protracted external doses**
  - **Doses much larger than those received by nuclear workers in other countries**
- **Substantial exposure from internally deposited plutonium**
  - **No other human data that are adequate for estimating cancer risks from plutonium**
- **Both male and female workers exposed**

Mayak Dosimetry

External exposure

- Monitored for external exposure with individual film badges

Plutonium exposure

- Dose estimates based on urine monitoring data
- Urine monitoring data available for only 40% of those with potential for plutonium exposure

Mayak Dosimetry

- Extensive collaborative effort of US and Russian scientists to improve both external and internal dose estimates
- Improved doses known as Doses-2008
- Most results in this presentation based on Doses-2005

Mayak worker doses (Doses-2005)

Mean external dose (Gy)

Mayak workers	0.54
IARC 15-country nuclear worker study	0.02

Mean internal plutonium dose to the lung (Gy)

Mayak workers	0.19
Sellafield workers (UK)	0.01

Results: External Dose

- **Analyses adjusted for plutonium exposure**
  - **Surrogate used for unmonitored workers**

- **Statistically significant increase in risk with increasing external dose for**
  - **All solid cancers**
  - **All solid cancers excluding lung, liver and bone**
  - **Leukemia**
  - **Lung cancer**

Shilnikova et al. 2003; Sokolnikov et al. 2008; Preston et al. 2010

Leukemia and External Dose

Years since dose received	ERR* per Gy
3 - 5 years	7.6 (3.2, 17)
5 + years	0.45 (0.1, 1.1)
5 - 10	0.3
10 - 20	0.8
20+	0.4

*Excess relative risk

Shilnikova et al. 2003

Results: External Dose

- Analyses based on improved dose estimates (Doses 2008) and updated mortality underway

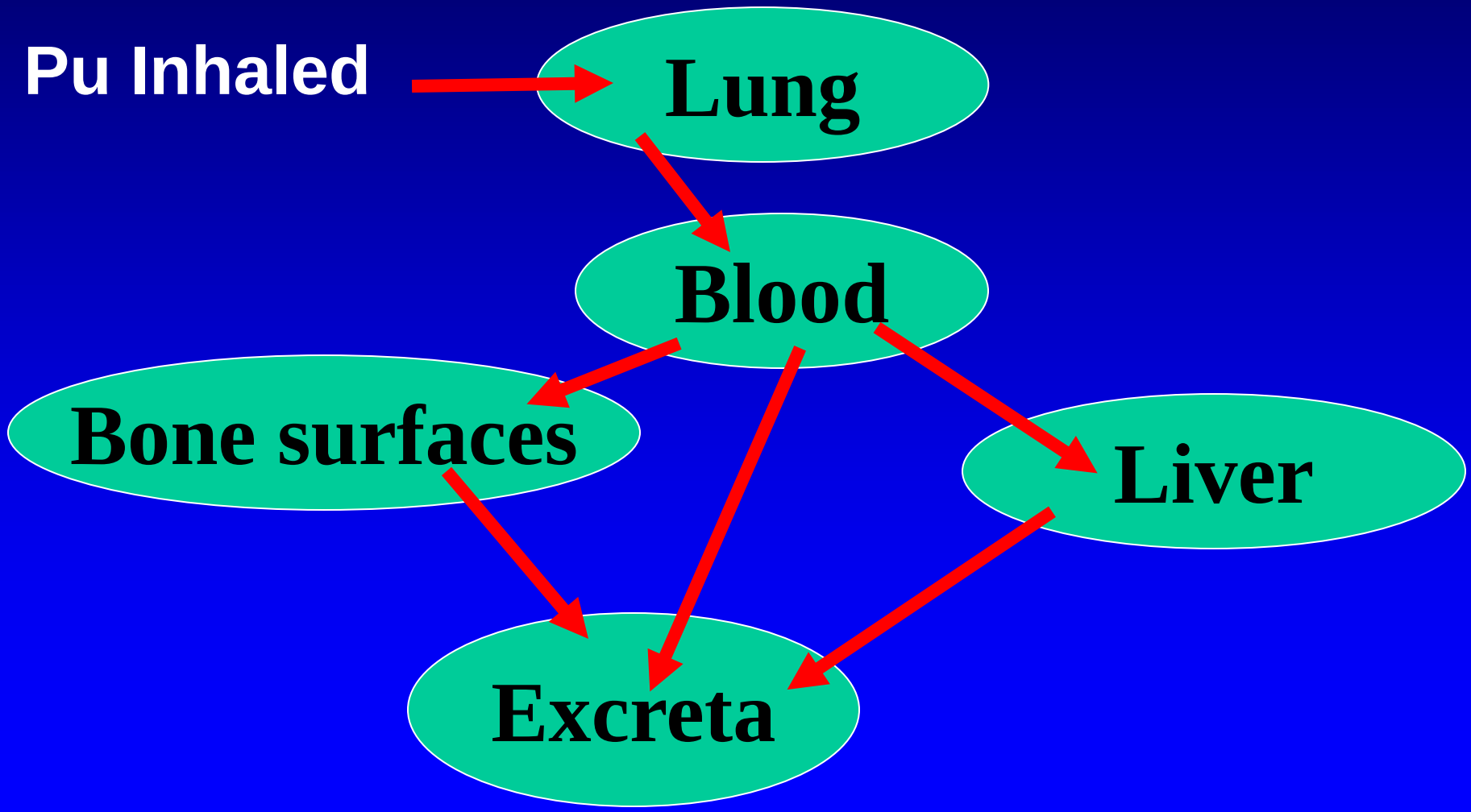
- Includes evaluation of site-specific cancer risks
  - External dose
  - Plutonium exposure

Plutonium: “The most hazardous substance known to man?”

Plutonium Concerns

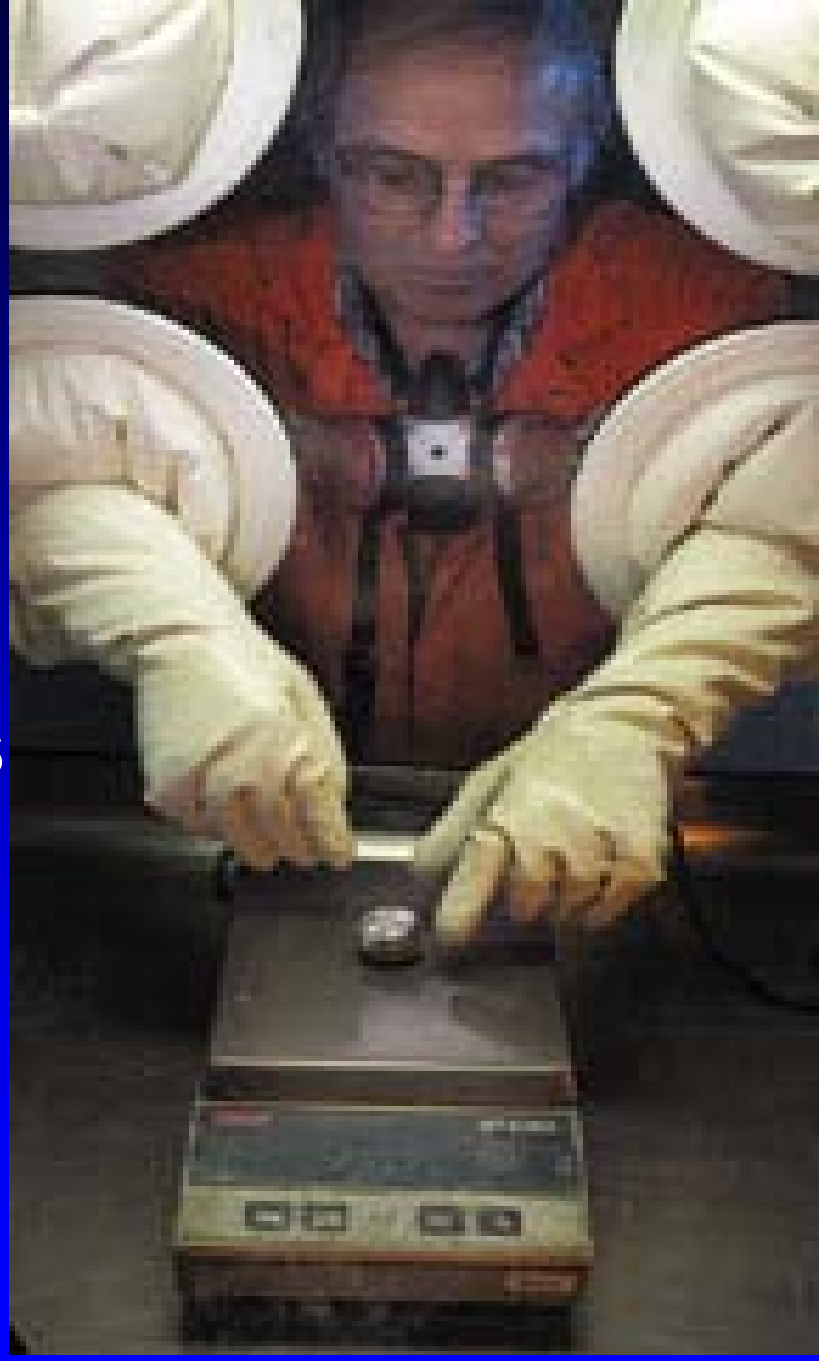
- **Occupational Exposure**
  - Plutonium production
  - Nuclear Fuel Reprocessing
  - Clean-up operations
- **General Public**
  - Reactor accidents
  - Nuclear wastes
  - Space accidents

An Overly Simple View of Inhaled Plutonium Dynamics



Studies of Workers Exposed to Low Doses from Plutonium

- US: Los Alamos, Rocky Flats Mound, Hanford
- UK: Sellafield



Studies of Workers Exposed to Low Doses from Plutonium: Summary

- Strong “healthy worker effect” (US)
- No clear evidence of adverse effects
- Sample sizes and exposures too small for meaningful risk assessment

Plutonium doses for Mayak and Sellafield workers

	Mayak	Sellafield
Mean dose (Gy) to		
Lung	0.19	0.010
Liver	0.27	0.005
Bone surfaces	0.98	0.036

Mayak Worker Results: Internal Plutonium Dose

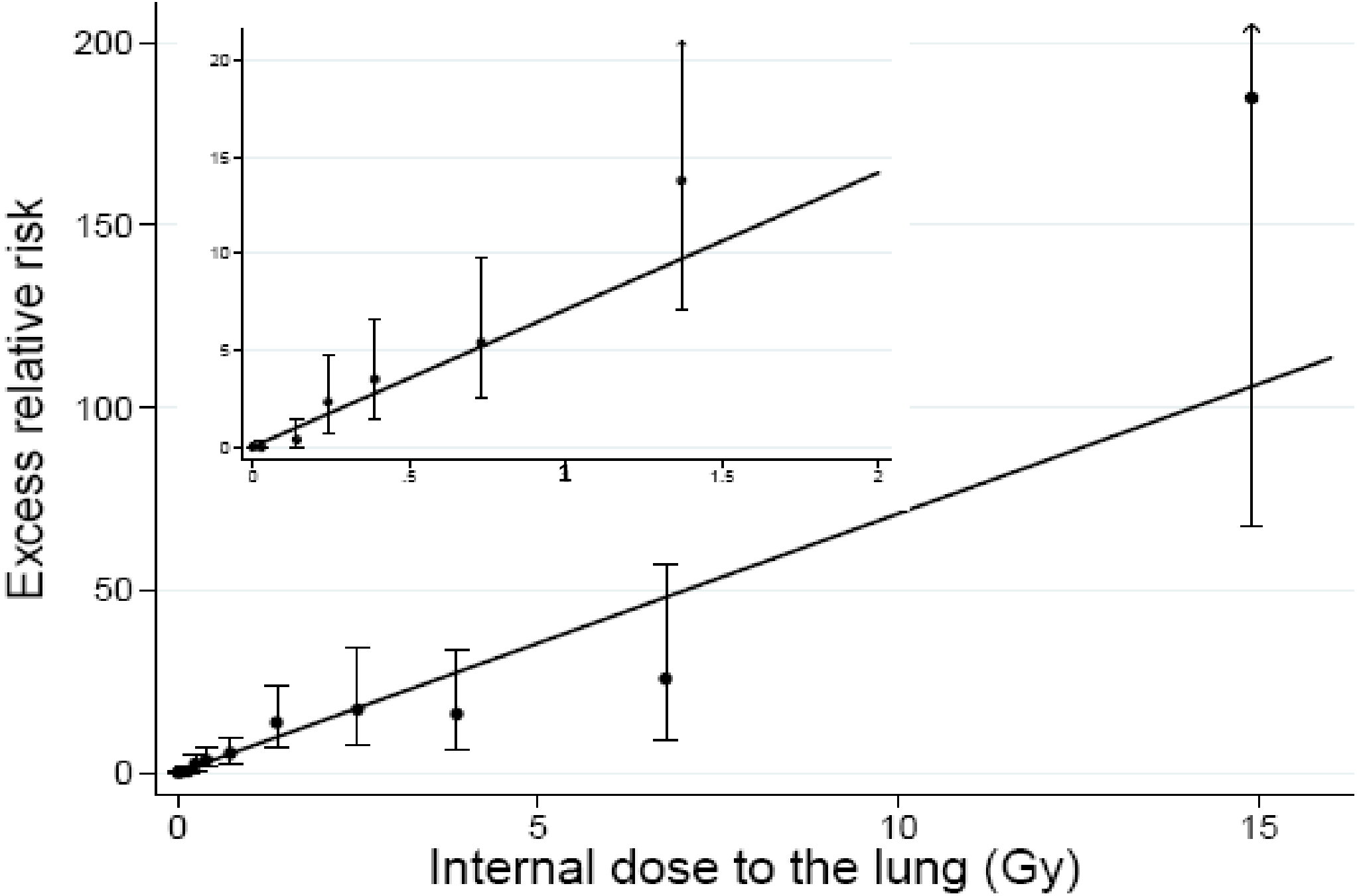
- Based on Sokolnikov et al. Int. J. Cancer 2008
- Doses-2005
- Follow-up through 2003
- Plutonium dose-response based on workers with plutonium doses that could be estimated
  - Monitored or never worked in radiochemical or reactor plants

Lung cancer: Plutonium dose-response

Lung Dose (Gy)	RR (95% CI)	Deaths
0	1.0	139
>0 - .1	0.98 (<1 - 1.3)	111
.1-	1.4 (<1 – 2.4)	16
.2-	3.3 (1.7 – 5.8)	14
.3-	4.5 (2.4 – 7.7)	14
.5-	6.4 (3.5 - 11)	15
1-	15 (8.1 - 25)	16
2-	18 (8.3 – 35)	8
3-	17 (7.1 - 35)	7
5-	27 (10 - 59)	6
10+	186 (69 – 466)	8

Estimates for males.
Estimates for females are a factor of 2.1 higher

Sokolnikov et al. 2008


Excess relative risk
200
150
100
50
0
0
5
10
15
Internal dose to the lung (Gy)
20
15
10
5
0
0
.5
1
1.5
2

Smoking in Mayak workers

- Smoking data obtained from medical records*
- 75% of males and 4.2% of females reported smoking
- RR for lung cancer by smoking status

	Males	Females
Non-smoker	1.0	1.0
Smoker	9.4 (6.2-15)	4.7 (2.1-9.1)
Unknown	4.7 (2.7-8.3)	1.5 (0.8-2.6)

*Available for 89% of males and 84% of females

Lung Cancer: Modification by sex

ERR per Gy for plutonium

Males: 7.1 (4.9 – 10)

Females: 15 (7.6 – 29)

Female/Male ratio = 2.1 (1.0 – 4.3)

Results shown are for attained age 60

Summary: Age effects for lung cancer

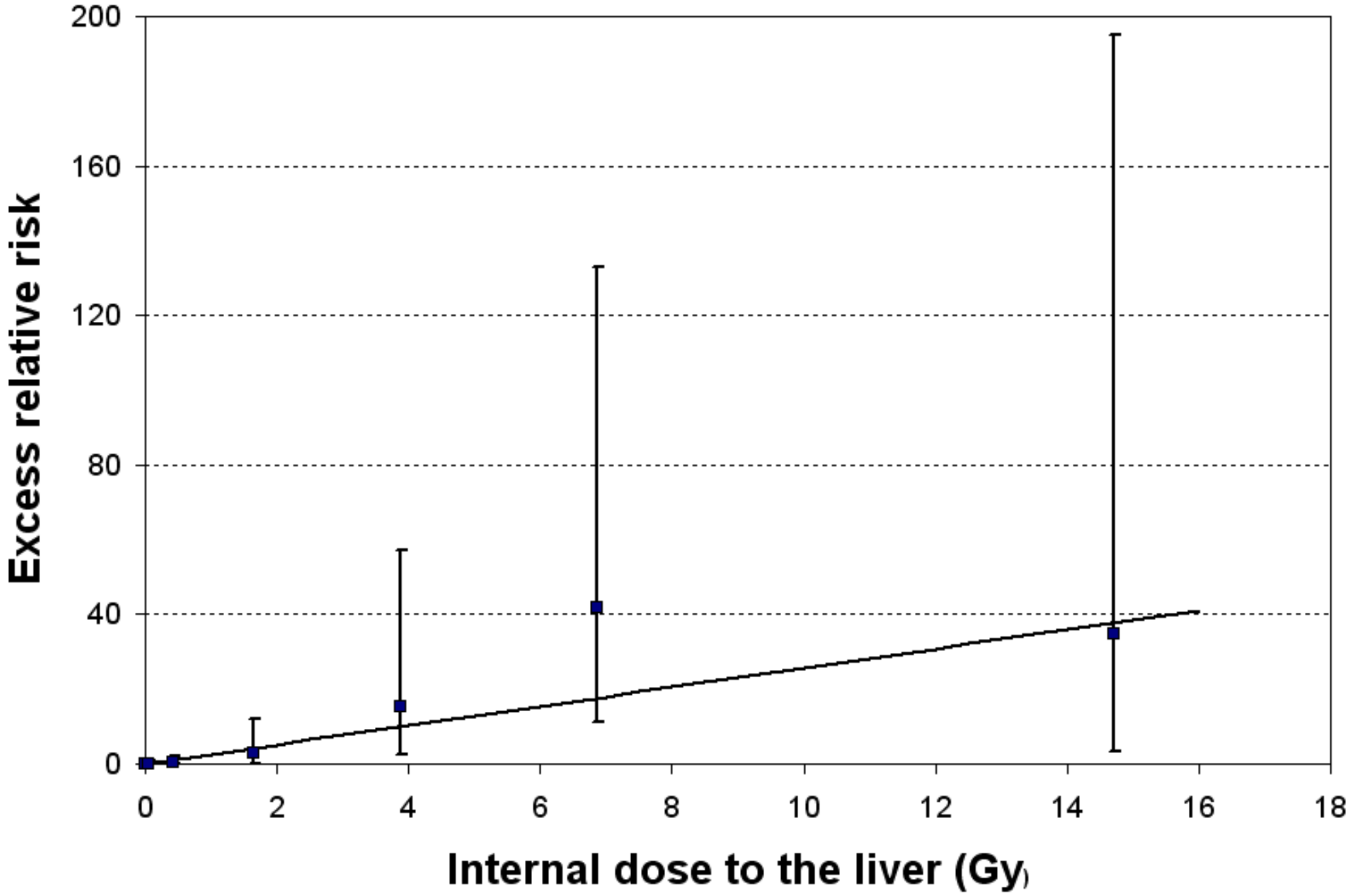
- ERR per Gy declined sharply with attained age
- Pattern very similar to that observed for underground miners (BEIR VI)
- Suggestion of decline in risk with age at first exposure

Liver cancer: Plutonium dose-response

Dose to liver (Gy)	RR (95% CI)	Deaths
0	1.0	14
>0 – 0.2	1.03 (<1 - 1.8)	9
0.2-	1.5 (<1 - 3.2)	2
1-	4.0 (1.2 - 13)	3
3-	16 (3.3 – 58)	3
5-	43 (12 – 134)	7
10+	36 (4.5 – 196)	2

Estimates for males
Estimates for females are a factor of 11 higher

Sokolnikov et al. 2008


200
160
120
80
40
0
Excess relative risk
0
2
4
6
8
10
12
14
16
18
Internal dose to the liver (Gy)

Bone cancer: Plutonium dose-response

Dose to bone surface (Gy)	RR (95% CI)	Deaths
0	1.0	5
>0 - 1	0.9 (<1 – 4.3)	3
1-	0.0 (0.0 – 8.7)	0
5-	0.0 (0.0 – 61)	0
10+	82 (17 – 338)	3*

*Doses of bone cancer deaths were 21, 37, and 85 Gy
Estimates for both sexes.

Sokolnikov et al. 2008

ERR per Gy for plutonium dose

	Males	Females
Lung:	7.1 (4.9 – 10)	15 (7.6 – 29)
Liver:	2.6 (0.7 – 6.9)	29 (9.8 – 95)
Bone:	0.8 (<0 – 5.2)	3.4 (0.4 – 20)

Sokolnikov et al. 2008

Shape of plutonium dose-response

	Power of dose (η)
Lung:	1.0 (0.8 – 1.2)
Liver:	1.3 (0.8 – 1.8)
Bone:	2.1 (0.8 – 3.8)

Power function: $\beta\ dose^{\eta}$

Limitations in Mayak Data

- For liver and bone cancer
  - Number of excess cases is small
  - Risk at low doses very uncertain
- Limited data on confounders
- Dosimetry
  - Uncertainties could affect both magnitude of risk and shape of dose-response

Uncertainties in Plutonium Dosimetry

- Imprecision in urine measurements
- Uncertainties in when plutonium exposure occurred and form of plutonium
- Uncertainties in biokinetic models and parameter values used to estimate deposition and clearance in organs of the body
- Models can only approximate behavior of plutonium in a given individual

Summary Comments on Mayak

- Mayak worker cohort is a unique resource for evaluating the risk of cancer from
  - Protracted external exposure
  - Plutonium exposure
- Recognize limitations

Radiation Worker Studies

- Nuclear workers exposed to low doses of external radiation
- Mayak nuclear workers
  - Exposed to high protracted external doses
  - Plutonium
- Medical and dental workers

Medical Radiation Workers

Population	Number of workers
US radiologists	6500
UK radiologists	2700
US technologists	146,000
US Army technologists	6600
Chinese x-ray workers	27,000
Danish radiation therapy workers	4200
Japanese technologists	12,200
Canadian radiation workers	73,100

Yoshinaga et al. 2004

Medical Radiation Workers

US technologists

- 146,000 radiologic tech.
- First employed 1926-82
- 73% female
- Survey data on disease incidence and cancer risk factors

Chinese x-ray workers

- 27,000 workers
- First employed 1950-80
- 20% female

Both cohorts

- Cancer excesses for early years identified
- Doses estimated
- Dose-response analyses underway

US RadiologicTechnologist Cohort

- **146,000 radiologic technologists 1926-82**
  - **73% females**

- **Health endpoints**
  - **Cancer mortality**
  - **Non-cancer mortality**
  - **Cancer incidence**
  - **Some benign diseases**
    - **Cataracts**

Collaborative study – NCI and U. of Minnesota

US Radiologic Technologist Cohort

- **Fractionated external exposure**
  - **Doses quite high in early calendar years (before 1950)**
- **Excesses for early years identified for**
  - **Breast cancer**
  - **Thyroid cancer**
  - **Melanoma**
  - **Basal cell carcinoma**
  - **Non-CLL leukemia**

Collaborative study – NCI and U. of Minnesota

US RadiologicTechnologist Cohort

- 3 surveys conducted

- Provide information on
  - Disease incidence
  - Work history and practices
  - Cancer risk factors
    - smoking,
    - physical activity
    - weight
    - several factors

Collaborative study – NCI and U. of Minnesota

US RadiologicTechnologist Cohort

- **Estimates of dose (and uncertainties) have recently been developed**

- **Make use of**
  - **Monitoring data**
  - **Survey data on work histories and practices**
  - **Historical information on occupational doses**

- **Dose-response analyses underway**

Collaborative study – NCI and U. of Minnesota

Radiation Worker Studies

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- Medical and dental workers

Thank you for your attention.

Questions?